UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,592	07/20/2001	Jonathan M. Friedman	389004/039 JJD/BO	1403

7590 02/11/2004

James F. Haley, Jr., Esq
c/o FISH & NEAVE
1251 AVENUE OF THE AMERICAS
50TH FLOOR
NEW YORK, NY 10020

EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,592	FRIEDMAN, JONATHAN M.	
	Examin r	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,37,39-53 and 61-69* is/are pending in the application.

4a) Of the above claim(s) *13 and 63-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-23,37,39-53,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23,37,39-53,and 61-69* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' arguments filed November 13, 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The new title and amendment to the specification have been acknowledged.

3. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are examined on the merits.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. This rejection is maintained with respect to claims 1-12, 14-23, 37, 39-53, 61, and 62, as recited in the previous office action mailed June 11, 2003.

7. This rejection is necessitated by Applicants amendments.

8. Specific to claims 1 and 48, lines 1-2, Applicant has amended said claims to read "A method of using parallel computational means..." in the preamble, which causes the said claims to be vague and indefinite, because claims 1 and 48 do not recite any active steps for performing parallel computational means for practicing the claimed method. Step (d) of said claims recites a computational step; however, it is unclear whether the computational step

requires parallel processing or not. Applicant is reminded that if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction (MPEP §2111.02). Clarification of the metes and bounds is required. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being directly or indirectly dependent from claim 1 or 48.

9. Claims 1 and 48, step (g) recites the limitation "the set of presumed values" in lines 8-9. There is insufficient antecedent basis for this limitation in the claim.

10. Specific to claims 1 and 48, step (e), line 3, the term "becomes" causes the claim to be vague and indefinite because it is unclear how each spherical harmonic spherical Bessel basis function becomes a Fourier representation. Does each spherical harmonic spherical Bessel basis function spontaneously become a Fourier representation, or due to some data analysis or data manipulation? Step (g) of claims 1 and 48 further causes the claim to be vague and indefinite because it is unclear how the calculation of the Fourier representation of each spherical harmonic spherical Bessel basis function is accomplished in step (g) when such step has been achieved in step (f). Clarification of the metes and bounds is required. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being dependent from claim 1 or 48.

RESPONSE TO ARGUMENT

11. Applicant argues, "step (f) (currently step (e)) involves a data manipulation step, a step which is distinguishable from the calculation of the Fourier representation of the entire unit

cell achieved in step (b). Applicant's argument has been fully considered and found to be unpersuasive because it is unclear how a spherical harmonic spherical Bessel basis function that represents an individual basis function centered at a specific position "becomes" a Fourier representation of basis function.

12. Specific to claims 1, steps (g) and (h), line 1; 39, line 5; 40, line 4; and 48, step (g), line 1, the term "complex-valued" causes the claims to be vague and indefinite because it is unclear what criteria is being used to consider that a coefficient is "complex-valued" (crystal structure of a complex comprising a receptor and a ligand or the difficulty of determining the coefficients). Clarification of the metes and bounds is required. Claims 2-12, 14-23, 37, 39-47, 49-53, 61, and 62 are rejected for being dependent from claim 1 or 48.

RESPONSE TO ARGUMENT

13. Applicant argues by pointed to support (page 11) which defines complex numbers by an equation with variables. Applicant's argument has been fully considered and found to be unpersuasive because it is unclear whether the complex values are the results of using said equation or the variables within the equation.

RESPONSE TO ARGUMENT

14. Specific to claims 2, line 5; and 9, line 3, the term "improvements" causes the claim to be vague and indefinite because it is unclear what is being improved (the process of modeling or the data generated from the process). Clarification of the metes and bounds are required.

15. Applicant argues the use of the term "improvements" is to refer to the improvement of the three-dimensional model structure data itself. Applicant's argument has been fully

considered and found to be unpersuasive because the use of the term "improvements" in said claims remains vague and indefinite.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

NEW MATTER

17. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. This rejection is necessitated by Applicants amendments.

19. Specific to claims 1 and 48, step (g), lines 6-9, the new limitation of "scale factors and correlation coefficients of the phase angle...are calculated at any one of the set of presumed values 0^{o} and 90^{o}"' is considered to be new matter. It is acknowledged that applicants discloses that only two choices of presume alpha angles for the SHSB-coefficient for Fsolo are necessary and the combination of two choices of Fsolo (each having a value for the presumed alpha phase angle set at either 0 or 90 degrees) (page 18, lines 4-9 and page 23, lines 5-11). The instant specification specifies it is only necessary to calculate two presumed values of α, 0^{o} and 90^{o}, which is different from the "calculated at any one of the set of presumed values 0^{o} and 90^{o}."

LACK OF ENABLEMENT

20. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the three-dimensional structure of a Staphylococcal aureus nuclease, does not reasonably provide enablement for any other molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

21. This rejection is maintained with respect to claims 1-12, 14-23, 37, 39-53, 61, and 62, as recited in the previous office action mailed June 11, 2003.

RESPONSE TO ARGUMENT

22. Applicant argues "the claimed invention is directed to methods that may be applied to any and all pre-existent X-ray diffraction data sets, irrespective of the manner by which they are derived. Applicant cites the MPEP § 2164 as directed cases involving predictable factors...a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty to argue that the claims are enabled to the full scope of the claimed invention. The examiner has not pointed to any scientific evidence to the contrary that the skilled artisan would be able to practice the full scope of the claimed invention. Applicant's argument has been fully considered and found to be unpersuasive due as discussed below.

23. The cited scientific literature (Drenth, J. and New Focus, Science, 2002) provided in the previous Office Action, mailed June 11, 2003, strongly supports that the art of protein

crystallization is an unpredictable art. Therefore, Applicant's argument via pointed to support in the MPEP directed to predictable factors is made moot.

24. As directed to the argument that "the claimed invention is directed to methods that may be applied to any and all pre-existent X-ray diffraction data sets, irrespective of the manner by which they are derived, the instant claims are not limited to any particular set of pre-existing X-ray diffraction data sets. Therefore, Applicant's argument has been made moot due the instant claims not support said argument.

25. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

26. It is re-iterated that the applicant has disclosed information to enable one skilled in the art to use the said method specific specifically for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease (Page 33, lines 21-25). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise

guidance for one skilled in the art to reliably use the said method. It is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). Accordingly, it would be unpredictable for one skilled in the art to use the said method to determine the three-dimensional structure of any other molecule beyond the ones of the instant case. In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to use the claimed invention on any other of predictable quality without undue experimentation.

27. Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61, and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining the three-dimensional structure of a Staphylococcal aureus nuclease using equations 1-12 (pages 10-14), does not reasonably provide enablement for determining the three-dimensional structure of a Staphylococcal aureus nuclease using any other mathematical equation. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

28. It is acknowledged that the applicant has disclosed information to enable one skilled in the art to use the said method specific specifically for determining the three-dimensional structure of a *Staphylococcal aureus* nuclease (Page 33, lines 21-25 and equations 1-12, pages 10-14). It would be unpredictable for one skilled in the art to use the said method to determine the three-dimensional structure using any other mathematical equation beyond the ones of the instant case. In light of the difficulty of the protein crystallization process as discussed above and the lack of guidance of using any other mathematical equations, it is, therefore, unreasonable to expect one skilled in the art to use the information disclosed for one specific crystal to use the claimed invention on any other of predictable quality without undue experimentation.

CLAIM REJECTIONS - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims 1-12, 14-23, 37, 39-53, 61, and 62 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Friedman (January 1999).

31. This rejection is maintained with respect to claims 1-12, 14-23, 37, 39-53, 61, and 62, as recited in the previous office action mailed June 11, 2003.

32. This rejection is necessitated by Applicants amendments.

RESPONSE TO ARGUMENTS

33. Applicant argue that Friedman does not anticipate every limitation of claims 1-12, 14-23, 37, 39-53, 61, and 62, more specifically, amended claims 1 and 48; because Friedman does not disclose the limitations of parallel computational means and/or scale factors and correlation coefficients of the phase angle of complex-value coefficient are calculated at any one of the set of presume values 0^o and 90^o. Applicants' arguments have been fully considered and fount to be unpersuasive as discussed below.

34. Specific to the limitation of parallel computational means in Applicant's argument, the said limitation has not been given any patentable weight due to the amended claims raise new vague and indefinite issue in amended claims 1 and 48 as discussed above. (See ¶ 6 of this instant Office Action).

35. Specific to the new limitation of scale factors and correlation coefficients of the phase angle of complex-value coefficient are calculated at any one of the set of presume values 0^o and 90^o. Friedman discloses the calculation of direct space convolution product involves (1) a single point by multiplication of the Fourier transform of each spherical harmonic basis function and outside of the spherical expansion zone, the value of the spherical harmonic basis function, S_{lmn}, is zero and the value of α_{lmn} is represented by the coefficient of S_{lmn} (page 12, column 2, lines 34 to page 13, line 18).

36. The above response and pointed to disclosure by Friedman support that the method of Friedman anticipates every limitation of claims 1-12, 14-23, 37, 39-53, 61, and 62.

37. It is re-iterated that Friedman (1999) discloses a method for interconverting three-dimensional molecular spatial information with spherical harmonic-Bessel representation and non-centrosymmetric crystalline arrays (Abstract etc.), as in claims 37 and 49.

38. The method of Friedman has been tested with a few macromolecular crystals of known structure (page 22, column 2, lines 44-45), as in claims 1, 48, step (a); 3; 16; and 50.

39. Exhaustive searches are performed to find the position and rotational orientation of a known molecule in a new crystalline packing arrangement based upon a measured X-ray diffraction pattern and the Fourier phase information associated with the diffraction pattern is initially unknown (page 10, column 1, lines 21-30), as in claims 4 and 51. The inclusion of a reference by Berikov et al. is not used as prior art but only as a reference to expand on the step of exhaustive searches. Berikov et al. disclose an exhaustive search method involving decision tree construction with a recursive algorithm (page 555, column 2, lines 1-11 and Figure 4).

40. The said method based upon orthogonal basis functions allows for two of the final three rotational degrees of freedom to be handled by FFT and for the final rotation to be calculated rapidly by multiplying spherical harmonic coefficients by a matrix. Friedman discloses the use software such as DOCK for modeling the docking of ligands into protein (page 11, column 2, lines 2-56), as in claims 1, 48, step (b); and claim 2, step (k).

41. A resolution limit of 3.0 A is used in the evaluation of the FFTs (page 14, column 2, lines 2-3), as in claims 1 and 48, step (c).

42. Two arbitrary geometric parameters, radius and position, are determined for the unit cell lengths and angles in terms of the Fourier expansion (page 12, column 1, lines 1-34), as in claims 1 and 48, steps (d) and (g); and claim 6.

43. The prescreen step reduces the number of translation points that need to be considered (page 13, column 2, lines 52-54), as in claims 1 and 48, step (e).

44. The interconversion between the spherical harmonic-Bessel representation and the Fourier representation can be calculated (page 10, column 1, lines 10-13), as in claims 1 and 48, step (f). Further, the valued of zero is considered in the said calculations (page 16, equations 6-8), as in claim 10.

45. Complex-valued coefficients, Fourier summations, indices are calculated according to equations 3-5 (pages 15 and 16), as in claims 1, 48, steps (h), (i), and (j); 7; 8; 9; 11; and 39-42.

46. The said method is designed to provide functional maxima or minima for each of the energy terms (page 21, column 2, lines 16-17), as in claim 2, step (l).

47. One may use the said method for non-overlapping spherical expansion zones (page 21, column 2, lines 38-45), as in claim 5.

48. Equations 6-8 are used for converting from a series of spherical harmonic coefficients to one of Fourier structure factor amplitudes and phases (page 16, lines 26-28), as in claim 12.

49. DEC-alpha-4000 workstation is being used data input and output (page 14, column 2, lines 11-17) and model being displayed (Figures 1 and 2), as in claims 14, 15, 17-23, 43-47, 52, 53, 61, and 62.

CONCLUSION

50. NO CLAIM IS ALLOWED.

51. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

52. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

53. This application contains claims 13 and 63-69 drawn to an invention nonelected with traverse in the previous Office Action, June 11, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

54. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

55. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

56. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

57. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (571) 272-0549 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
2/9/04

ARDIN H. MARSCHEL
PRIMARY EXAMINER